REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1, 2, 7, 19, 26, and 30 are being amended, as discussed below. Support for these amendments can be found throughout the specification as-filed, including the original claims. No new matter is being added.

Claims 3 and 4 are requested to be canceled without prejudice or disclaimer.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 1-46 are now pending, and claims 15-17, 21-24, 29, 31-38, and 40-46 are withdrawn from consideration. At least claims 15-17, 21-24, 29, and 31-38 should be rejoined, because they are the same statutory class of invention as claim 1, and unity of invention is believed to exist, as noted in Applicants' amendment of October 5, 2005. Thus, claims 1-14, 18-20, 25-28, 30, and 30 are pending and being examined on the merits, and at least claims 1-24 and 26-39 should be examined together.

I. Claim Objections

The Office Action objects to claim 7, because the claim recites "α-1, and 4-fucosyl-transferase." The Office Action states that the "and" "[a]t the end of the claim should be deleted."

Applicants have amended claim 7 to delete the "and" as requested by the Office Action. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

II. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Office Action rejects claims 2, 26, and 30 under 35 U.S.C. § 112, ¶ 2, as allegedly indefinite. Each of these grounds of rejection is addressed below.

A. Claim 2

The Office Action rejects claim 2 under 35 U.S.C. § 112, ¶ 2, as allegedly indefinite for reciting "wherein said cell also comprises at least one gene encoding an enzyme capable of modifying an endogenous precursor, said enzyme being identical to or different than the enzyme of claim 1." According to the Office Action, "it is unclear if the gene being recited must be recombinantly introduced or if the claim is intended to include endogenously encoded genes." Office Action at 3. The Office Action also objects to the recitation of "enzyme of claim 1," as allegedly unclear.

While not acquiescing in the propriety of the rejection, Applicants have amended claim 2 to remove the language deemed objectionable by the Office Action. Accordingly, Applicants respectfully request withdrawal of this ground of rejection as moot.

B. Claim 26

The Office Action rejects claim 26 under 35 U.S.C. § 112, ¶ 2, because claims 26 is allegedly "incomplete as depending from claim 25."

While not acquiescing in the propriety of the rejection, Applicants have amended claim 26 to make it depend from claim 1 rather than canceled claim 25. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

C. Claim 30

Claim 30 stands rejected under 35 U.S.C. § 112, ¶ 2, as allegedly indefinite, because the specification allegedly lacks a definite of the term "glucose precursor." According to the Office Action, "the scope of compounds which could be considered 'glucose precursors' is enormous and impossible to define without complete knowledge of all metabolic pathways present in a microorganism." Office Action at 3. Applicants respectfully traverse this ground of rejection.

While not acquiescing in the propriety of the rejection, Applicants have amended claim 30 to delete the language deemed objectionable. Accordingly, Applicants respectfully request that the rejection be withdrawn as moot.

III. Claim Rejections – 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 1-14, 18-20, 26-28, 30, and 39 stand rejected under 35 U.S.C. § 112, ¶ 1, as allegedly lacking written description support. Each of the rejection is addressed below.

1. Claim 30

Claim 30 stands rejected under 35 U.S.C. § 112, ¶ 1, as allegedly lacking written description support. The Office Action states that the specification "fails to provide support" for the phrase "culturing occurs in the presence of a glucose precursor."

While not acquiescing to the propriety of the rejection, Applicants have deleted the language allegedly lacking written description support. Accordingly, Applicants respectfully request that the rejection be withdrawn as moot.

2. Claims 1-14, 18-20, 26-28, 30, and 39

Claims 1-14, 18-20, 26-28, 30, and 39 stand rejected under 35 U.S.C. § 112, ¶ 1, as allegedly lacking written description support. According to the Office Action, "[p]racticing the methods of the claims requires detailed knowledge of the biosynthetic pathways for the synthesis of any desire oligosaccharide, knowledge of the source of all enzymes necessary for such synthesis, knowledge of the metabolic/catabolic pathways to present the microorganism to be used and detailed knowledge of how these factors are interrelated such that one obtains the desired results." The Office Action argues that such detailed knowledge is lacking from the specification. Applicants respectfully traverse this ground of rejection.

The specification contains a sufficient description of the claimed invention to demonstrate possession of the claimed invention in view of the knowledge common in the art. Indeed, "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed," and a genus can be described by describing a representative number of species. Here, the specification contains an extensive description of the genes, precursors, and species of bacteria that can be used to practice the claimed invention, as discussed in Applicants' amendment of October 5, 2005 at pages 18-19. This description is supplemented by actual working examples describing the production of different oligosaccharides in *E. coli* cells. Thus, the specification contains a complete description of the claimed invention demonstrating possession of the claimed invention.

The Office Action argues that the specification lacks adequate written description, because oligosaccharides and their synthetic pathways are "highly complex" and that microorganisms in general produce oligosaccharides that differ from *E. coli* oligosaccarides using pathways that are "poorly defined." Office Action at 5-6. However, Applicants note that the claims have been amended to specify that the cell is a bacterial cell and that the exogenous precursor is selected from the group consisting of lactose, sialic acid, α-galactoside, and β-galactoside. In addition, biosynthetic pathways for producing oligosaccharides are known in the

art. Given the description in the specification and the knowledge of the skill in the art, one of skill in the art would readily recognize that Applicants were in possession of the claimed invention at the time of filing. Accordingly, the claimed are supported by an adequate written description.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

B. Enablement

Claims 1-14, 18-20, 25-28, 30, and 39 stand rejected under 35 U.S.C. § 112, ¶ 1, as allegedly lacking enablement. According to the Office Action, "the specification, while being enabling for methods of making lacto-N-neotetraose or polylactosamine from lactose using *Lac Z E. coli* transformed with the *Neisseria gonorrhoeae* LgtA and LgtB genes, does not reasonably provide enablement for methods of making any oligosaccharide from any exogenous precursor in any bacterium." Office Action at 6. Applicants respectfully traverse this ground of rejection.

While not acquiescing in the propriety of the rejection, Applicants have amended the claims to specify that the cell is a bacterial cell and that the exogenous precursor is selected from the group consisting of lactose, sialic acid, α-galactoside, and β-galactoside. Thus, the claims are no longer directed to methods involving **any** cell and **any** precursor and instead are directed to methods involving bacterial cells, such as *E. coli*, and the four types of precursors.

One of skill in the art could readily practice the claimed invention without undue experimentation based on the specification and the information known in the art. Indeed, the specification contains an extensive description of the genes, precursors, and species of bacteria that can be used to practice the claimed invention, as discussed above. This disclosure is supplemented by actual working examples using *E. coli.* to produce a variety of different oligosaccharides. In addition, one of skill in the art is aware of different oligosaccharide biosynthetic pathways and can readily apply that knowledge to practice the claimed invention.

Accordingly, one of skill in the art can practice the claimed invention without undue experimentation.

The Office Action argues that the specification does not enable the claimed invention, because the specification does not enable production of oligosaccharide in **any** cell. However, the present claims are not directed to any cell but instead are directed to "bacterial" cells. The specification provides working examples using *E. coli* cells. One of skill in the art could readily adapt these specific teachings to bacterial species other than *E. coli*. Accordingly, a skilled artisan could practice the claimed invention without undue experimentation.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

IV. Claim Rejections – 35 U.S.C. § 102

Claims 1-14 and 26 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bettler *et al.*, GLYCOCONJUGATE JOURNAL 16:205-212 (1999). According to the Office Action, Bettler anticipates the claims by allegedly disclosing an oligosaccharide using *LacZ*⁻ E coli transformed with a gene encoding chitin pentaose synthase and an LgtB gene encoding an β-1,4-galactosyltransferase from exogenously provided glycerol. Applicants respectfully traverse this ground of rejection.

Bettler does not teach or suggest the claimed invention, because Bettler does not teach or suggest one of the recited exogenous precursors. Specifically, the Office Action argues that Bettler teaches glycerol as an exogenous precursor, but glycerol is not one of the exogenous precursors recited in the claims.

In addition, Bettler does not teach or suggest a method for producing an oligosaccharide using an internalized exogenous precursor, as claimed. Indeed, Bettler fails to teach or suggest the use of glycerol, or any other compound, as an exogenous precursor. Instead, glycerol is

disclosed as the carbon source. Employing glycerol as a carbon source was known in the art and does not teach or suggest the use of an exogenous precursor as presently claimed. *See* spec. at page 10, lines 5-14.

For at least this reason, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

V. Claim Rejections – 35 U.S.C. § 103

Claims 18-20, 27, 28, 30, and 39 stand rejected under 35 U.S.C. § 103 as allegedly obvious. Each of the specific grounds of rejection is addressed below.

A. Claims 18-20, 27, 28, and 39 – Bettler in view of Kozumi

Claims 18-20, 27, 28, and 39 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Bettler in view of Kozumi. According to the Office Action, one of skill in the art would be motivated to combine Bettler and Kozumi, because Bettler "clearly teach the advantages of production of a desired oligosaccharide intracellularly in a growing *E. coli* culture." Office Action at 9. Applicants respectfully traverse this ground of rejection.

One of skill in the art would have no motivation to combine Bettler and Kozumi, much less any expectation of success. Lactose transport is an energy dependent process, and it was known in the art that rapid uptake of sugars by lactose permease disrupts membrane function, possibly by causing collapse of the membrane potential. *See* Wilson *et al.*, BIOCHIM BIOPHYS ACTA 649(2):377-84 (1981) (Exhibit A); Dykhuizen *et al.*, J. BACTERIOLOGY 135(3):876-82 (1978) (Exhibit B); and Ahmed *et al.*, J GEN MICROBIOL 129(8):2521-29 (1983). This phenomenon, which results in growth inhibition and eventually cell death, is known as "lactose killing." Given this knowledge in the art, a skilled artisan would have no reason to combine the teachings of Bettler and Kozumi, much less have an expectation of success. Indeed, such an

approach would be expected to kill the cultured cells. In fact, Kozumi's process does in fact result in death of the cells, as discussed in Applicants' October 5th Amendment.

Applicants own work verifies that skilled artisans were reluctant to investigate the internalization of lactose by the lactose permease in LacZ$^-$ strains growing on glycerol because of the lactose killing problem. Specifically, Mr. Samain, one of the present inventors, spent several years investigating possible ways to internalize glycosyltransferase acceptors in living bacteria. The first system employed, which used sugar derivatives with groups to enable passive diffusion, produced interesting results, but was not very efficient. Next, Mr. Samain investigated the use of O-acetylated derivatives, but this system simply did not produce useful results. Finally, Mr. Samain turned to internalization of lactose using lactose permease in a LacZ$^-$ strain growing on glycerol. This system was surprisingly to be successful, at least in part because lactose was added in a continuous manner at a very low rate to avoid the lactose killing problem. Thus, there was a strong prejudice in the art against practicing the claimed invention due to the well-known lactose killing problem.

Finally, most people working in the oligosaccharide synthesis field have a background primarily in either chemical or biochemical arts. These individuals have a limited understanding of bacterial physiology and tend to view bacterial as simple catalysts for oligosaccharide synthesis. Given this background, skilled artisans would be unlikely to arrive at the claimed invention, which required an understanding of bacterial physiology.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

B. Claim 30 – Bettler in view of Kozumi in further view of Johnson and Gotschlich

Claim 30 stands rejected under 35 U.S.C. § 103 as allegedly obvious over Bettler in view of Kozumi in further view of Johnson and Gotschlich. According to the Office Action, Bettler in

view of Kozumi fails to teach production of "lacto-N-neotetraose from lactose using a bacterium transformed with a β-1,3-N-acetyl-glucosaminyltransferase and a β-1,4-galactosyltransferase gene." Applicants respectfully traverse this ground of rejection.

Bettler in view of Kozumi do not teach or suggest the claimed invention, as discussed above, and Johnson and Gotschlich fail to remedy this deficiency. For at least this reason, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date May 30, 2006 By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicants
Registration No. 35,264